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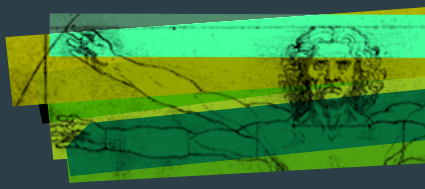
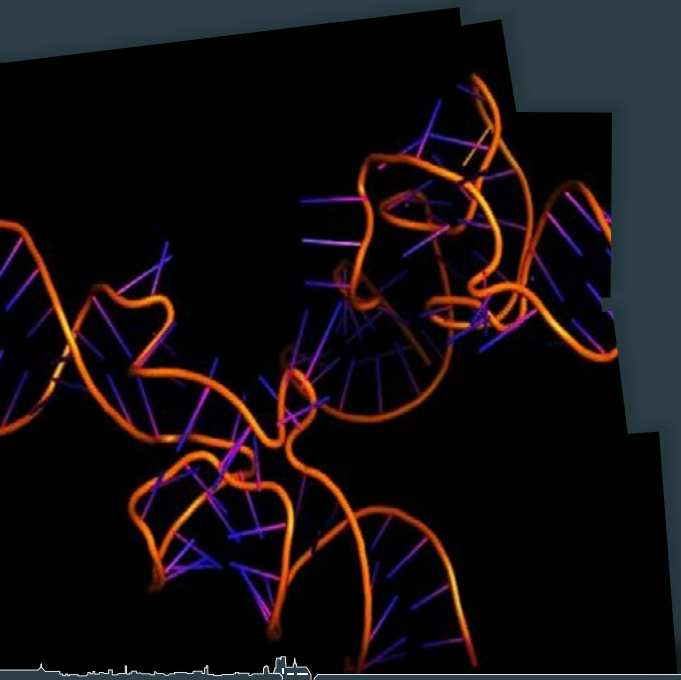
ORLÉANS | 2017



22-23 March 2017

Messenger RNA therapeutics: advances and perspectives



LOCATION

Hôtel Dupanloup
1, rue Dupanloup
45000 Orléans - France

CONVENORS

Dr Sohail Akhter

LE STUDIUM RESEARCH FELLOW FROM Pharmaceutical Science at Faculty of Pharmacy, Jamia Hamdard University, New Delhi, India

IN RESIDENCE AT Centre de Biophysique Moléculaire (CBM), UPR 4301 (Molecular Biophysics Center, CNRS) Orleans, France

Pr Chantal Pichon

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LE STUDIUM Loire Valley Institute for Advanced Studies

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ABSTRACTS

Messenger RNA therapeutics: advances and perspectives

CONVENORS

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Maurine Villiers, Events & Communication Assistant

LE STUDIUM Loire Valley Institute for Advanced Studies • Région Centre-Val de Loire • FR

EDITO

Created in 1996 on the CNRS campus in Orleans La Source, LE STUDIUM has evolved to become a multidisciplinary Loire Valley Institute for Advanced Studies (IAS), operating in the region Centre-Val de Loire of France. LE STUDIUM has its headquarters in the city centre of Orleans in a newly renovated 17th century building. The amazing facilities are shared with the University of Orleans. In 2014 new developments and programmes linked to the smart specialisation of the Centre-Val de Loire region came to strengthen existing IAS cooperative relationships with the local and the international community of researchers, developers and innovators.

LE STUDIUM IAS offers to internationally competitive senior research scientists the opportunity to discover and work in one of the IAS's affiliate laboratories from the University François-Rabelais of Tours, the University of Orleans, National Institute of Applied Sciences (INSA) Centre Val de Loire and ESAD Orléans, as well as of nationally accredited research institutions located in the region Centre-Val de Loire (BRGM, CEA, CNRS, INSERM, INRA, IRSTEA). Our goal is to develop and nurture trans-disciplinary approaches as innovative tools for addressing some of the key scientific, socio-economic and cultural questions of the 21st century. We also encourage researchers' interactions with industry via the IAS's links with Poles of Competitiveness, Clusters, Technopoles, and Chambers of Commerce etc.

LE STUDIUM has attracted over one hundred and sixty LE STUDIUM RESEARCH FELLOWS, LE STUDIUM RESEARCH CHAIRS and LE STUDIUM RESEARCH PROFESSORS for long term residencies. In addition to the contribution in their host laboratories, researchers are required to participate in the scientific life of the IAS through attendance at monthly interdisciplinary meetings called LE STUDIUM THURSDAYS and gathering members of the regional scientific community and industries.

For the period 2015-2020, LE STUDIUM operates with an additional award from the European Commission in the framework of the Marie-Skłodowska Curie Actions (MSCA) with the programme MSCA-COFUND for the mobility of experienced researchers. This co-funding instrument increases the number of LE STUDIUM fellowships to be awarded each year.

Researchers are also invited and supported by the IAS to organise, during their residency and in collaboration with their host laboratory, a two-day LE STUDIUM CONFERENCE. It provides them with the opportunity to invite internationally renowned researchers to a cross-disciplinary conference, on a topical issue, to examine progress, discuss future studies and strategies to stimulate advances and practical applications in the chosen field. The invited participants are expected to attend for the duration of the conference and contribute to the intellectual exchange. Past experience has shown that these conditions facilitate the development or extension of existing collaborations and enable the creation of productive new research networks.

The present LE STUDIUM CONFERENCE devoted to Messenger RNA therapeutics: advances and perspectives is part of the Biopharmaceuticals ARD 2020 Programme and is the 57th in a series started at the end of 2010 and listed at the end of this booklet.

We thank you for your participation and wish you an interesting and intellectually stimulating conference. Also, we hope that during these two days some of you will see an opportunity to start a productive professional relationship with LE STUDIUM Loire Valley Institute for Advanced Studies and laboratories in the region Centre-Val de Loire.

Professor Ary Bruand

Chairman
LE STUDIUM

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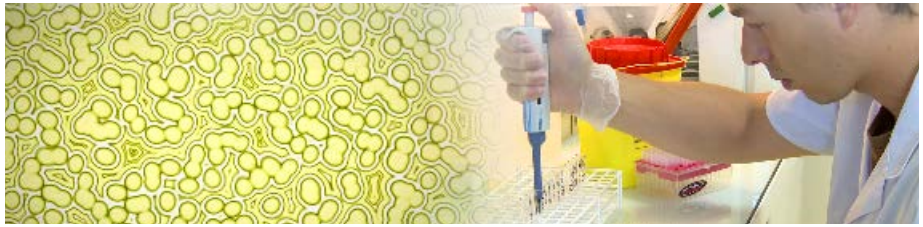
ARD 2020
BIOPHARMACEUTICALS



A drug is any substance or composition presented as having properties for treating, preventing or diagnosing disease in humans or animals. Whereas biopharmaceuticals in the strict sense of the term, are molecules that have the characteristic of being produced from living organisms or their cellular components. These molecules are intermediate between chemical drugs and living biologics.

The proportion of biopharmaceuticals in the drug market should increase from 20% in 2014 to more than 40% by 2020. The region Centre-Val de Loire is at the cutting edge of research in the pharmaceutical sector, the Regional Council provides with a high level of funding for 6 years of increased research efforts and to facilitate innovative inter-sectorial industrial development and partnerships for socioeconomic development beyond 2020.

The ARD 2020 Biopharmaceuticals (Biomédicaments) programme aims to further develop and strengthen the region Centre-Val de Loire biopharmaceuticals industry by capitalising on the recognised capabilities of the multidisciplinarity research teams from the regional research institutions.

The programme aims to:

- Develop a flagship research and development pole on biopharmaceuticals in the region Centre-Val de Loire.
- Configure the biopharmaceuticals field by inter-sectorial development and innovation in the pharmacy/health sectors through start-ups, SMEs including established local and regional based multinational companies.
- Promote the transfer of technologies/competences to existing businesses.

The Biopharmaceuticals programme focuses on the design and biosynthesis of molecules for preclinical and clinical development by including the search for synergies with conventional chemically synthesised drugs. The programme involves working with a wide spectrum of molecules (vaccines, therapeutic antibodies, nucleic acids...) with the need for a diverse range of competences and the involvement of teams with complementary expertise.

The researchers present in the region Centre-Val de Loire, working in the disciplines of life sciences, are invited to participate and work in synergy, for inter-sectorial development and innovation, in the pharmacy/health sectors to deliver socio-economic outcomes.

WORDS OF THANKS

Dear Colleagues,

On behalf of the committees, it is my pleasure to welcome you in Orléans for the conference on "**mRNA therapeutics advances and perspectives**" organised by Centre de Biophysique Moléculaire (CBM), CNRS and LE STUDIUM, Orleans under the framework of regional Biopharmaceuticals ARD2020 Programme. This conference aims to distribute the knowledge of fundamental and applied research in the field of messenger RNA-based therapeutics.
We brought together more than 25 internationally well renowned scientists and pioneers in different aspects of mRNA s to provide an interdisciplinary forum for participants to discuss and exchange the most recent innovations and practical challenges in this field. We are much honoured to have a key note opening speech by **Pr Kris Thielemans** (Vrije Universiteit Brussel, Brussels, Belgium). We are very grateful to the invited speakers; **Pr Philippe Barthelemy**, Université de Bordeaux (France); **Pr Nicolai Bovin**, Synthaur LLC, Moscow – Russia; **Pr Rebecca Cox**, University of Bergen, Norway; **Dr Mustafa Diken** - Translational Oncology Institute Freiligrathstr, Mainz, Germany; **Dr Jonathan Finn**, Intellia Therapeutics, USA; **Dr Carlos A. Guzman**, HZI, Braunschweig, Germany; **Pr Jonathan Heddle**, Jagiellonian University, Poland; **Pr Jacek Jemielity**, University of Warsaw, Poland; **Pr Michael Kormann**, University Children's Hospital Tübingen, Tübingen, Germany; **Dr Ine Lentacker**, Ghent University, Belgium; **Dr Kenneth C. McCullough**, Institute of Virology and Immunology, Switzerland; **Dr Patrick Midoux**, Centre de Biophysique Moléculaire, CNRS, France; **Dr Bruno Pitard**, In Cell Art, France; **Pr Nicola Tirelli**, University of Manchester, United Kingdom; **Pr Richard Weiss**, University of Salzburg, Austria, who share their innovations and will give new understandings to the conference participants. Last but not the least we truly appreciate **Pr Philippe Roingeard** (Université de Tours, France) for his very interesting public lecture. Organization of this event is very much a team effort. I want to particularly thank all of the members of conference committee and my sincere acknowledgement to the team working at LE STUDIUM, who have delivered a satisfying event with ease.

For your participation, finally, we wish you all have a great time of this exciting conference socially and scientifically.

Sincerely Yours,

Pr Chantal Pichon

Pr Chantal Pichon

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Chantal Pichon is Full Professor at exceptional class- the highest rank of French university- at the University of Orleans, France where she is currently the head of the Institute of Life Sciences and Chemistry for Life. She has completed a *Ph.D.* in Cellular Biology and Microbiology (1991) at the University of Aix-Marseille before spending 2 years at the AFRC, Cambridge-UK.
Chantal Pichon is performing her research activities at the Center for Molecular Biophysics of CNRS where she is coordinating the department of Cell Biology and Innovative therapies. Advanced molecular approaches of biochemistry, cell and molecular biology are exploited in conjunction with cell and animal models to decipher molecular biological processes occurring under physiological or pathological conditions. Efforts are made to identify new therapeutic targets to fight against cancer, aging and central nervous system diseases; to develop tissue models with an adequate microenvironment; and to conceive therapeutic strategies development of chemical-based vectors for DNA, RNA (mRNA, replicons and siRNA). The team is the pioneer of histidine-based nanoparticles and has developed novel strategies to improve uptake by chemical targeting and/or ultrasound trigger, the nuclear import and the cytosolic diffusion.

Dr Sohail Akhter

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IN RESIDENCE AT: Centre de Biophysique Moléculaire (CBM), UPR 4301 (Molecular Biophysics Center, CNRS) Orleans - France

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Dr. Sohail Akhter is working as a senior Le Studium fellow at Centre de Biophysique Moléculaire (CBM)-CNRS/ University of Orléans, UPR4301, Orléans, France. His present research focuses on the optimization of novel synthetic nano-biopharmaceuticals of nucleic acids for therapeutic vaccination against cancer. His past research experiences include Senior Postdoc research fellow at U.S. Food and Drug Administration (US-FDA)/The Centre for Drug Evaluation and Research (CDER)/DPQR, USA and research associate at the Department Pharmaceutics, Utrecht Institute of pharmaceutical sciences, Utrecht University, Netherlands. He received team excellence award-2015; U.S. Food and Drug Administration (US-FDA)/CDER/DPQR for this work on novel non-destructive chemometric method and PAT tools and Nanomedicine European technology platform fellowship in the year 2013. He has completed his PhD in Pharmaceutical Sciences (pharmaceutics specialization) as a DBT/CSIR research Fellow and Masters in Pharmacy (pharmaceutics specialization) from Jamia Hamdard University, New Delhi, India. Dr. Akhter has authored more than 50 manuscripts in high impact journals. His research interests involve development and characterization of nanostructured drug delivery systems, nanomedicines, application of bio-materials in drug delivery & targeting, biopharmaceutics, drug/ nanoparticles metabolism, biodistribution and bioanalysis.

mRNA-lipoplexes for dendritic cells transfection: Toward the rational design of cationic lipid, co-lipids and combination thereof

Sohail Akhter*[1,2], Marine Dubuisson[1], Lucie Pigeon[1], Cristine Goncalves[1], Mathieu Berchel[3], Paul-Alain Jaffres[3], Midoux Patrick[1], Chantal Pichon[1]

[1]Cell Biology and Innovative Therapies, Centre de Biophysique Moléculaire, CNRS UPR4301, Orléans, France. [2]Le Studium Loire Valley Institute for Advanced Studies, Centre-Val de Loire region, France. [3]Université de Bretagne Occidentale, UMR CNRS 6521 - UFR Sciences et Techniques, Brest, France

Short-term transient gene expression due to its cytoplasmic translation, rapid onset, short duration of expression and greater efficiency, particularly in non-dividing cells made mRNA a potential new class of bio-medicament for vaccination against cancer. Very vulnerable to enzymatic degradation and anionic nature however made its direct delivery practically challenging and thus required biological or chemical carriers. Cationic liposomes preferred as the choice among the chemical vectors in nucleic acids delivery (termed as lipoplexes) due to ease of chemical variability and production, non-immunogenicity, and relatively non-toxic nature of its lipid composition. There is no "one- chemistry/size-fits-all" answer in nucleic acids delivery- transfection efficiency relationship and therefore new lipids are regularly being explored to improve the transfection efficiency of lipoplexes. Herein, we present the novel imidazole containing lipophosphoramidate based amphiphilic lipids as effective mRNA transfection agents intended for dendritic cells (DCs)-based cancer vaccination. These lipids formed stable nano-sized (80 nm-150 nm; polydispersity index within 0.2) highly positively charged (50 mV-120 mV) liposomes capable of efficient complexation of mRNA. We observed good correlation between the fusogenicity at acidic pH and the mRNA DCs transfection of imidazole bearing lipophosphoramidate lipid combinations. Moreover, lipophosphoramidate cationic lipids combination with DOPE gave fair number of mRNA positive cells with exceptionally high protein expression.

Pr Philippe Barthelemy

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Barthélémy received his doctorate in chemistry from the University of Montpellier II, France in 1993. He was then a postdoctoral fellow at Emory University in the group of Pr Fredric Menger (Lavoisier Grant and Emory Fellowship). In 1995 he was appointed as a temporary lecturer at the University of Avignon and as Associate Professor at the same University in 1996. P. Barthélémy worked also as a Visiting Associate Professor at Duke University in 2001. In 2005 he was appointed as full Professor at the University of Bordeaux Segalen. He is leading the "ChemBioPharm" team of the INSERM U1212. Philippe Barthélémy was Vice President of the University of Bordeaux Segalen (2011-2013).

Nucleic acid chemistry for nanomedicine

[1]Univ. Bordeaux, ARNA laboratory, F-33000 Bordeaux, France.

[2]INSERM, U1212, ARNA laboratory, F-33000 Bordeaux, France.

The combination of nucleic acids chemistry (e.g., nucleoside, nucleotides, oligonucleotides) with supramolecular principles provides an efficient and powerful approach to prepare well-defined systems with tunable physico-chemical properties and functions. We develop new nano-systems based on nucleic acids chemistry for i) drug delivery applications (therapeutic, theranostic), and ii) tissue engineering. This communication will present novel "smart" nucleic acid derivatives (nucleolipids, lipid-oligonucleotide conjugates) developed in our lab [1].

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Pr Nicolai Bovin

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- CSO in Synthaur LLC, Moscow, Russia

Academic research group of N.Bovin works in the following areas: synthesis of oligosaccharides and neoglycoconjugates; supramolecular chemistry; glycan/protein and glycan/glycan interaction; natural antibodies. Synthaur LLC is company focussed on medicinal chemistry, particularly: influenza therapy and diagnostics, transfusion and transplantation, cancer diagnostics and targeting, antibacterial coatings.

Search of glycan as a vector for delivery of vaccine particles to dendritic cells

Nicolai Bovin[1], Eugenia Rapoport[1], Sergey Khaidukov[1], Kenneth McCullough[2]

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[2] Institute of Virology and Immunology, Sensemattstr. 293, CH-3147, Mittelhäusern, Switzerland

Dendritic cells (Dc) play a crucial role in innate and adaptive immune response; targeting of antigen to this minor population of cells is promising strategy for improvement of vaccines against bacterial and viral infections. For the targeting, we explored as recognition of glycans by Dc lectins; for the glycan selection we primarily profiled glycan-binding potency with a library of 230 fluorescent glycoprobes. At the first run, eight glycoprobes (capable of binding > 15% circulating Dc (circDc) and "non-classical" monocytes (pre-moDc)) were selected, and further used for more detailed profiling the isolated circDc and pre-moDc. Additionally, we compared monocytic Dc and circDc. It was found that: 1) the glycan-binging profiles of circDc and moDc are similar but not identical; 2) the highest percentage of positive circDc was observed for GalNAcα1-2Galβ (A_{di}), Neu5Acα2-8Neu5Acα2-8Neu5Ac (Neu5Acα)$_3$ and three mannose-reach glycans, whereas pre-moDc preferentially bound 4'-O-Su-LacdiNAc. Relying on the literature data on specificity of Dc lectins, we suggested that the partners of selected glycans in case of circDc are macrophage galactose binding lectin, siglec-7 and dectin-2. Taking into consideration competition of glycan-vectors with glycans of Dc glycocalyx, we believe that A_{di} and (Neu5Ac)3 are the best potential vectors for Dc targeting.

Pr Rebecca Cox

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Rebecca Cox is Professor of Medical Virology and Head of the Influenza Centre at the University of Bergen, Norway. Rebecca Cox completed her Ph.D. in 1995 at the London Hospital Medical College, University of London, UK with Professor John Oxford on the immune response to Influenza vaccines in man. She then had post doc. positions at Guys Hospital, UK and at the University of Bergen under Professor Lars Haaheim. In 2000 she was appointed lecturer in Medical Virology, University of Bergen and in 2008 she became appointed head of the Influenza Centre with a current staff of 10 and from 2009 Professor in Medical Virology. Her research career has focused on evaluating and developing improved influenza vaccines and is currently funded by the European Union, Norwegian Research Council, Centre of Excellence as The Jebsen Centre for Influenza Vaccines and the Department of Health. The main areas of research are preclinical research and development of novel adjuvants and influenza vaccines, clinical trials of new influenza vaccines from phase I to IV with focus on detailed characterisation of the immune response. Rebecca has over 70 peer-reviewed publications in journals or book chapters Rebecca is a member of The Norwegian Influenza Pandemic committee, which provides advice to the Ministry of Health and Care Services. She has served as an expert reviewer for investigator-initiated trials for the European Union and for influenza vaccines to the vaccine industry. She has been invited to the World Health Organization meetings on pandemic vaccines and Broad Spectrum and Long-lasting Immune Responses and served as an advisor to the European Medicines Agency on Scientific Aspects of Serological assays. She has been an active member of ISIRV and currently sits on the board of ISIRV where she is keen to promote education of the next generation of scientists.

Human clinical studies of influenza vaccines

Novel avian and swine influenza viruses constitute a pandemic threat and the development of effective vaccines is a global priority. Evaluation of novel influenza vaccines requires extensive preclinical studies including demonstration of the protective efficacy before entering phase I trial. In this presentation, human clinical trials of novel pandemic (e.g. H5, H7 and H1) vaccines will be discussed including the kinetics, longevity and cross reactivity of the humoral and cellular immunological responses.

Dr Mustafa Diken

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Dr. Mustafa Diken received his Ph.D. in tumor immunology from Johannes Gutenberg University, Mainz and is currently serving as the Deputy Director of Immunotherapy Development Center at TRON and the Deputy Head of Immunotherapies Department at Biontech RNA Pharmaceuticals. His research focuses on the development of novel cancer vaccines based on antigen-encoding messenger RNA (mRNA) and the elucidation of immunomodulatory mechanisms for cancer immunotherapy. His other scientific interests include assay development for preclinical testing of cancer vaccines. Dr. Diken is also the scientific secretary of the Association for Cancer Immunotherapy (CIMT), a non-profit organization aimed at advancing cancer immunotherapy.

Systemic delivery of mRNA vaccines for potent cancer immunotherapy

Immunotherapy has evolved as a promising alternative to conventional treatments against cancer. Thanks to its unique characteristics, mRNA can act not only as a source for antigen but also as an adjuvant for activation of the immune system. Vaccination with tumor antigen-coding RNA has been shown to be capable of efficiently inducing T cell responses and anti-tumor immunity in preclinical models and RNA-based vaccines are currently being tested in clinical trials with promising results. We have recently developed a novel class of systemically administered nanoparticulate RNA vaccines (RNA-LPX) acting by body-wide delivery of encoded antigens to APCs and simultaneous initiation of a strong type I IFN-driven immunostimulatory program. RNA-LPX vaccines mimic the infectious non-self and thus mobilize both adaptive and innate immune mechanisms. The simple but highly versatile design allows vaccine preparation with any type of RNA-encoded antigen and may thus be regarded as a universally applicable, first-in-class vaccine platform for cancer immunotherapy.

Dr Jonathan Finn

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Jonathan (John) Finn worked in the gene therapy field for >17 years, working with a wide range of gene therapy modalities. He originally trained with Pieter Cullis (CSO INEX, Professor UBC) and Ian Maclachlan (CSO Protiva Bio, CTO Tekmira) applying non-viral delivery systems to the field of oncology before transitioning to the viral vector field, gaining experience with both Adenoviral (Jonathan Bramson, McMaster University) and AAV gene therapy applications (Katherine High/Valder Arruda, CHOP). Prior to joining Intellia, John served as Director of Research and Development at Arthrogen B.V., a company focused on the development of gene therapy for the treatment of joint diseases, where he worked with both AAV and extracellular vesicle based delivery systems. John is an active member of the ASGCT, serving on multiple committees, and was the recipient of the 2013 ESGCT Young Investigator Award. At Intellia, John's team has made significant progress on the development of efficient non-viral and viral delivery systems for CRISPR/Cas9 components, an essential step in the successful translation of genome editing to the clinic.

Robust *In Vivo* Gene Editing in Mouse Hepatocytes with Systemic Lipid Nanoparticle Delivery of CRISPR/Cas9 Components

John Finn, Mihir Patel, Amy Rhoden Smith, Lucinda Shaw, Maddy Younis, Corey Ciullo, Reynald Lescarbeau, Jessica Seitzer, Jaqueline Growe, Chris Dombrowski, Patrica Lowden, Kenneth Manning, Walter Strapps, Thomas Barnes, David V. Morrissey

There is considerable interest in the therapeutic potential of CRISPR/Cas9-mediated gene editing to treat a wide variety of genetic diseases; however, clinically viable delivery of CRISPR/Cas9 components presents an obvious challenge. Effective and safe delivery of CRISPR/Cas9 components, whether based on viral or non-viral delivery vehicles, would require specific targeting of a tissue or cell type; and brief half-life in order to minimize potential off-target activity and innate and humoral immune responses. In addition, the ability to re-administer the therapy to attain stable, therapeutically relevant levels of gene editing would be an advantage. With these requirements in mind, we have explored the use of lipid nanoparticles (LNPs) for delivery of CRISPR/Cas9 components to the liver to mediate editing of target DNA within hepatocytes. Cas9 mRNA and chemically synthesized gRNA specific to the mouse transthyretin gene (*Ttr*) were co-formulated into LNPs, and administered to mice *via* intravenous tail vein injection. Various parameters were explored, including the nature of the guide RNA (sgRNA vs. dgRNA & chemical modification), the dosing regimen, and molecular strategy (single target site vs. two-target site micro-deletion). We found that the best results were obtained with a chemically modified single guide co-formulated with Cas9 mRNA. We were able to achieve a median dose-dependent editing of up to 55% of the gene copies in liver biopsies. A corresponding dose-dependent reduction of serum transthyretin protein levels was seen, with a decrease of up to 80%. The levels of editing across liver lobes were in general highly consistent. Notably, the DNA repair patterns in liver were distinctly different from those seen in cell lines using the same *Ttr*-specific gRNA. These results demonstrate that therapeutically meaningful levels of *in vivo* CRISPR/Cas9-mediated gene editing can be obtained with a completely synthetic and scalable single-agent system, and suggest that the treatment of liver-based genetic disease with CRISPR/Cas9 will be clinically viable.

Dr Carlos A. Guzman

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C. A. Guzman graduated in Medicine and become Board Certified in Medical Bacteriology in Argentina. Later, he graduated as Doctor of Medicine and Surgery and obtained his Doctorate in Microbiological Sciences (University Genoa, Italy). In 1994 he became Head of the Vaccine Group (German Research Centre for Biotechnology, Germany). In 2005 he was appointed Head of the Department of Vaccinology and Applied Microbiology (HZI), becoming later also APL-Professor at the Medical School and Member of the Centre for Individualized Infection Medicine (Hannover). His work was instrumental for developing new adjuvants and antigen delivery systems, leading to more than 200 research articles.

Adjuvantation with cyclic-di-nucleotides: an efficacious strategy to tailor humoral and cellular immune responses to vaccination

Vaccination is the most powerful and cost-efficient tool to fight infectious diseases. Traditional vaccines consist of attenuated or inactivated pathogens, whereas subunit vaccines are based on purified antigens. However, subunit vaccines are usually poorly immunogenic, making essential the use of adjuvants. Most available vaccines are also needle-based, whereas if would be preferable to exploit noninvasive strategies. Unfortunately, only a few adjuvants are presently available for human use. These adjuvants are poor inducers of mucosal immunity, exhibit limited capacity to tailor T-helper (Th) and cytotoxic responses, and they are often not customized for poor responders (e.g. elderly). Our adjuvant development program led to the discovery of several well-defined immune modulators, which are now produced by chemical synthesis. These adjuvants are also active when administered by the mucosal or transcutaneous route as well as in poor responders. One promising compound class comprises the cyclic-di-nucleotides (CDNs), which are prokaryotic signaling molecules with strong immune modulatory effects on dendritic cells and macrophages by activation of the type I interferon and TNF pathways. Co-administration of CDNs with purified antigens induces strong humoral and cellular responses with a balanced Th1/Th2/Th17 phenotype, and cytotoxic cells. Influenza A virus vaccines adjuvanted with CDNs confer protection against virus challenge in different preclinical models. CDNs can also enhance responeses to RNA-based vaccines. This new generation of fully synthetic adjuvants with well-defined molecular targets represents a powerful tool for the rational design of vaccines or immune therapies.

Pr Jonathan Heddle

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Jonathan Heddle studied Pharmaceutical Science at The University of Nottingham, UK before moving to The University of Leicester to work on the antibacterial target DNA gyrase and its inhibitors. He then moved to Japan as a Japan Society for Promotion of Science Special Research Fellow where he first studied structural biology before setting up his own laboratory increasingly researching bionanoscience first at Tokyo Institute of Technology and then at RIKEN. He recently moved back to Europe to head a lab at the Malopolska Centre of Biotechnology, Jagiellonian University, Poland where he continues to research bionanoscience and topoisomerases.

Building Artificial Nanoscale Structures With Proteins

In nature proteins can act as nanomachines, carrying out a multitude of tasks and have evolved specialised structures finely adapted to do so. Designing and building *artificial* protein structures is a first step towards the goal of producing artificial "bionanomachines" which could have great potential in a number of fields including medicine. This area of research is still in its infancy but some progress has been made. In our own work we have used the bacterial, ring-shaped protein "TRAP", that binds mRNA, as a useful building block: We have carried out biochemical and structural studies of this protein and built a number of artificial nanoscale structures using it. For example we have been able to modify TRAP so that it stacks to form a self-assembled nanotube. More recently we found that certain TRAP mutants are able to undergo an unusual reaction in the presence of gold nanoparticles and form a large-capsid like hollow sphere. The structure of the sphere and its properties are still under investigation but its high stability and hollow nature suggest potential uses in drug delivery amongst others.

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Jacek Jemielity got his Ph. D. in chemistry in 2002 at the Faculty of Chemistry, University of Warsaw. Then he moved to Division of Biophysics, Faculty of Physics, University of Warsaw as an assistant professor. Since 2013 he is the leader of Laboratory of Bioorganic Chemistry at Centre of New Technologies, University of Warsaw. His research is focused on development of methods for nucleotide synthesis, chemical modification of nucleic acids and applications of nucleotides and modified RNA in studies on gene expression and potential therapeutic applications.

Chemical modifications at 5′ end of mRNA: towards mRNA-based gene therapy.

Cap analogs are chemically modified derivatives of the unique cap structure present at the 5′ end of all eukaryotic mRNAs. Continuing advances in understanding of the biological functions of the cap and the consequences of the disruption of these processes – resulting in serious medical disorders – have opened new possibilities for therapeutic applications of synthetic cap analogs. The medicinal potential of cap analogs has emerged in several areas. The most promising and the most advanced one is mRNA-based gene therapy. It has been generally assumed that mRNA is not stable enough for therapeutic applications. Significant progress in engineering mRNA stability and in vivo translational efficiency made such applications possible. The presentation will be focused on recent advances in chemical modification of the cap structure and applications of cap analogs in the studies on cap-dependent processes, which eventually led to improvement of existing methods of protein expression for therapeutic purposes.

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Michael S.D. Korman has studied biology in Munich, Germany, at the renewed universities Ludwig-Maximilians-University and Technical University Munich, which then lead to his work as a PhD student in the group of Prof. Michael Kabesch, with focus on the genetic influence of atopic asthma. After finishing his PhD with summa cum laude he worked for three years in the BioFuture group of PD Dr. Carsten Rudolph, where he learnt all basic and advanced possibilites of gene therapy of the lungs. He then settled over to the University of Tübingen, becoming one of the youngest junior professors at the University. So currently he is an Assistant Professor for Translational Genomics and Gene Therapy in Pediatrics at the Universit of Tübingen, Germany, and works at the University Children's Hospital - Section I - Pediatric Infectiology and Immunology.
Dr. Kormann serves as an Editor, Reviewer and Editorial Board member for many scientific journals and books. He is a member of several scientific societies, including the German CF Association and American Society of Gene and Cell Therapy. Dr. Kormann has a total of 24 Publications with more than 800 citations. He has currently three European-wide patents and has won several national and international awards and prizes for his work.

Therapeutic application of chemically modified mRNA in mouse models of severe lung diseases

Surfactant Protein B (SP-B) deficiency and Cystic Fibrosis (CF) are severe, fatal inherited diseases affecting the lungs of ten thousands of people, for which there is currently no available cure. Recent studies of our group were the first to demonstrate life-saving efficacy of repeated pulmonary delivery of chemically modified messenger RNA (mRNA) in a mouse model of congenital SP-B deficiency. By incorporating balanced amounts of modified nucleotides to mimic endogenous transcripts, we developed a safe and therapeutically efficient vehicle for lung transfection that eliminates the risk of genomic integration commonly associated with DNA-based vectors. We also assessed the delivery of mRNA-encoded site-specific nucleases to the lung to facilitate targeted gene correction of the underlying disease-causing mutations. In comprehensive studies, we show that a single application of nucleases encoded by nucleotide-modified RNA (nec-mRNA) can generate in vivo correction of terminally differentiated alveolar type II cells, which more than quadrupled the life span of SP-B deficient mice. Now we aim to further develop this technology to enhance the efficiency and safety of nec-mRNA-mediated in vivo lung stem cell targeting, providing an ultimate cure for congenital respiratory diseases by permanent correction.

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Ine Lentacker obtained her Master's degree in Pharmaceutical Sciences at Ghent University in 2004. In the same year she became a doctoral fellow of the Fund for Scientific Research-Flanders (FWO-Vlaanderen) at the Ghent Research Group on Nanomedicines under supervision of Prof. Stefaan De Smedt. During her PhD she developed the concept of nanoparticle loaded microbubbles for ultrasound guided drug delivery. In 2009 she became a post-doctoral fellow of the Fund for Scientific Research-Flanders. During that time, she participated in two European FP7 Research Projects (Sonodrugs and Arise). In her current research projects she focuses on the elucidation of sonoporation mechanisms and the potential of mRNA nanoparticles and mRNA loaded microbubbles for cancer immunotherapy.

Ultrasound triggered mRNA delivery to dendritic cells: towards an *in vivo* cancer vaccination strategy?

Increasing knowledge on the crucial role of dendritic cells (DCs) in the initiation of immunity has launched a new field in cancer immunotherapy: DC vaccination. By loading a patient's DCs ex vivo with tumor antigens and injecting them as a vaccine, antitumor immune responses can be induced. As an alternative to the currently used strategies for antigen-loading of DCs, we propose mRNAsonoporation. By adding mRNA-loaded microbubbles to DCs and exposing them to ultrasound, the microbubbles locally implode and deliver their mRNA payload to the DCs. As such, this project aims to use theranostic mRNA-loaded microbubbles (MBs) for ultrasound-guided, ultrasound-triggered antigen-loading of DCs within the lymph nodes *in vivo*. mRNA-loaded MBs were prepared by attaching mRNA-lipid complexes to lipid MBs via avidin-biotin linkages. MBs loaded with mRNA encoding a tumor antigen (ovalbumin, OVA) were used to sonoporate murine DCs in vitro. These mRNA-sonoporated DCs were then used as therapeutic vaccines in E.G7-OVA-bearing mice. In vitro mRNA-sonoporation of murine DCs revealed transfection efficiencies up to 27%. The potential of this technique was further assessed *in vivo* by vaccinating E.G7-OVA-bearing mice with sonoporated DCs. When mRNA sonoporated DCs were used, tumor growth was significantly reduced and even regressed in 30% of the animals. Moreover, rechallenge with E.G7-OVA or MO4 tumor cells, did not lead to tumor growth, indicating long-lasting and antigen specific immunological protection. A CEUS study in dogs showed the MBs rapidly drained to the lymph nodes after s.c. injection. Currently we are evaluating the *in vivo* potential of this strategy in freshly anesthetized pigs.

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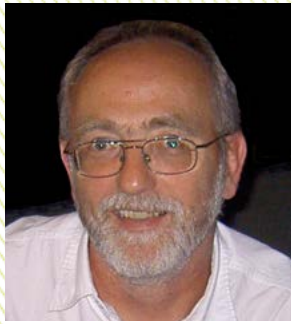

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Ken McCullough studied virology and immunology at Queen's University of Belfast, where he carried out his PhD studies on measles virus persistence relating to SSPE, and also studying the demyelinating effects of sera from multiple sclerosis patients. He moved on to the Animal Virus Research Institute (Institute for Animal Health) in England, studying virus infections of macrophages. In 1986 he moved to Switzerland, investigating the influence of cytokines on enzootic pneumonia. Since 1989, he has worked at the Institute of Virology and Immunology (formerly the Institute of Virology and Immunoprophylaxis, and before that the Swiss Federal Vaccine Institute). There, he continued his interest in virus infections of macrophages, and also dendritic cells. This was extended into studies on dendritic cell endocytosis, which led to the invention of the first biodegradable nanoparticulate delivery systems for self-amplifying RNA (replicon RNA). The latter became his main them of research, from which the UniVax consortium arose; although retired, he continues as coordinator of UniVax, promoting nanoparticulate delivery of self-amplifying RNA vaccines against influenza virus.

Dendritic cells and Self-Amplifying Replicons Vaccines: the Univax consortium

Protective immune defences are dependent upon critical roles played by dendritic cells (DCs). A critical parameter for efficacious vaccination is the essential role of DCs. Being the most efficient of the antigen-presenting cells, they are important targets for vaccine delivery, particularly when considering RNA vaccines. At the same time, this renders DCs important targets for virus infection. Studies in these areas led to successful development of targeted vaccine delivery, including synthetic virus-like particle (SVLP) and nanoparticulate-RNA vaccines. A major consideration is DC endocytosis, whereby the different endocytic routes influencing the outcome. Rapid clathrin-mediated endocytosis likely favours degradative pathways. Slower processes – macropinocytosis, caveolar endocytosis and retrograde transport to endoplasmic reticulum – relate more to the processing rates leading to antigen presentation by DCs. These pathways are also influential in promoting the initiation of virus replication following infection. DC endocytosis of RNA viruses and RNA vaccines must lead to cytosolic translocation of the RNA for translation, relating to the process of antigen cross-presentation.

One can learn from observations on virus infections and cross-presentation for delivering RNA vaccines. Studies with mRNA vaccines have shown the value of incorporating cationic entities promoting endocytic vesicle perturbation to facilitate cytosolic translocation. Whilst successful with mRNA vaccines, these RNA molecules have limited half-life within the cell. In order to enhance the duration of RNA vaccine translation and the generation of antigen, self-amplifying RNA are currently under study. These are derived from viral RNA genomes rendered defective by removal of structural genes essential for virus assembly. When derived from positive-strand viruses, they do function as mRNA, but are much larger and more complex molecules. Moreover, they encode not only for vaccine antigen, but also for proteins involved in the replication of the RNA, hence their description as self-amplifying and the term replicon.

Accordingly, recent advances in nanoparticulate delivery have been applied with self-amplifying replicon RNA (RepRNA), providing efficient delivery to DCs and promoting replicon-encoded antigen translation. Through realising the important relationships between DC endocytic pathways and induction of immune responses, delivery of RepRNA vaccines to DCs offers high value for development of future synthetic vaccine platforms.

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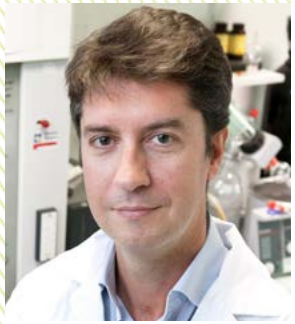
Patrick MIDOUX is Research Director C1 at Inserm, Deputy General Director of Centre de Biophysique Moléculaire since 2008.
He carried out doctoral studies (Doctor es Sciences) at Centre de Biophysique Moléculaire and University of Orléans. In 1981 he focused his research in drug delivery notably by using monoclonal antibodies and glycoconjugates. Since 1993 his research activity is centered around gene and mRNA delivery with a special emphasis on the design of synthetic vectors. From 1999 to 2016, he was scientific team leader of "Nucleic acids transfer by synthetic vectors". He has published more than 120 peer reviewed articles and filed 10 patents. His h-index is 40 (Web of sciences).

LPR-based mRNA vaccine delivery systems

Dendritic cells (DCs) are the most important component of immunity, playing a critical role in antigenic presentation. Since the pioneering works of Sullenger and Gilboa, preclinical and clinical studies have been extensively tested for induction of antigen-specific immune responses against cancer cells or viruses by injection of autologous DCs transfected ex vivo with mRNA encoding specific antigens. Direct administration of synthetic mRNA encoding antigens is more attractive for vaccination of large population and clinical trials have been already initiated in patients with melanoma, renal cell carcinoma, prostate cancer and non-small-cell lung metastatic carcinoma. In this context, the transfection of DCs with synthetic mRNA encoding antigen is becoming increasingly important for the design of innovative vaccines. One major challenge to be tackled is their targeting to DCs. It is crucial to develop delivery systems that in vivo protect mRNA from degradation, help internalization in DCs and favour intracellular delivery in the right compartment. Since mRNA translation occurs in the cytosol, the transfection of DCs with synthetic mRNA avoids the necessity of mRNA to pass the nuclear envelope. For this purpose we have developed mRNA lipopolyplexes (LPR) which are ternary complexes formed between liposomes-polymer-mRNA. Liposomes and polymers carried histidine or imidazole moieties allowing translocation of mRNA in the cytosol. Using the B16F10 melanoma murine model, we demonstrated that LPR and mannosylated LPR are efficient mRNA delivery systems to induce a specific immune response against cancer cells. Mannosylated LPR significantly exert curative responses in mice vaccinated after initial tumor inoculation. These encouraging results demonstrated that DC targeting with mannosylated LPRs gave a sufficient stimulatory response to promote a therapeutic anti-cancer immune response, and could be considered for anti-cancer vaccine in Humans.



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Dr Pitard received his Ph.D in 1995 from Paris University for his work on membrane protein reconstitution intoliposomes in Commissariat à Energie Atomique (CEA) (Saclay, France) and Institut Curie (Paris, France).
He graduated from Compiègne University with an engineer and a master of biochemical engineering degree.
He started his career in 1995 at Rhône-Poulenc Rorer (now Sanofi, Vitry sur Seine, France) on the Gene Therapy program. Then, he worked at Sanofi-Pasteur (Lyon, France) on the DNA vaccine program.
He is Scientific Director at Centre National de la Recherche Scientific (CNRS)/University of Nantes, France.
He has invented new concepts for the safe and efficient intracellular delivery of complex drugs including nucleic acids (mRNA, siRNA, DNA) and proteins (antibodies, transcription factors, enzymes...).
He has contributed to more than 80 publications and 17 patents on nucleic acids and protein formulations.
He is Associate Editor of the journal "Current Gene Therapy" published by Bentham science Publishers.
He has been member during 12 years of the scientific advisory board of the French cystic fibrosis foundation "Vaincre La Mucoviscidose" (Paris, France).
He created and launched in 2005 with a Nobel Laureate the Biopharmaceutical company InCellArt (Nantes, France).

Bioinspired delivery systems for mRNA vaccines and medicines

Curing diseases via mRNA delivery is a very promising approach. Non-formulated mRNA do not reach sufficient level of protein expression thus delivery systems are developed to increase the efficacy of this therapeutic strategy. Among these systems, the category of supramolecular transfection agents appeared to be of particular interest. The objective of this talk is to present the state of the art of synthetic delivery systems, resulting from a self-assembly process with the mRNA to deliver. We will describe two different classes of molecules we synthesized and used depending not only on the nucleic acids and especially mRNA but mostly on the final intended use, either for therapy or vaccine applications.

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Kris Thielemans was trained as an MD at the Vrije Universiteit Brussel (VUB), spent some years in the Laboratory of Dr. R. Levy at the Department of Oncology at the Stanford University Medical School (Ca, USA) and obtained a PhD degree. Harnessing the immune system to combat cancer has been his major interest since then. He manages the Laboratory of Molecular and Cellular Therapy (LMCT) at the VUB for more than 30 years focusing on immune-therapeutic translational research and therapeutic vaccine development, including clinical trials for the treatment of cancer and HIV. He is founder and CSO of the spin-off company eTheRNA Immunotherapies NV to develop and implement mRNA based immunotherapy.

TriMix technology for mRNA based vaccination

Modification of dendritic cells (DC) with mRNA allows their loading with tumor antigens and their functional programming. To reprogram immature DC towards potent antigen (Ag) presenting cells, we designed a set of molecules that mimic closely activation of these cells during the initiation of an adaptive immune response. We provide 3 molecular adjuvants: mRNA coding for a constitutive active variant of TLR4, mimicking TLR-4 activation; CD40L mRNA, mimicking the 'licensing' of DCs when Th cells and DCs interact and CD70 to provide an extra stimulus for the priming of $CD8^+$ T cells and inducing their proliferation and survival. The mixture of these three mRNA's is referred to as 'TriMix'.

mRNA encoding the full-length tumor specific or associated antigens is used to direct the immune system to the desired targets. To enhance a broad immune response and provide help to the CTLs, we ensure HLA-class-I and class-II presentation by modifying the antigen sequence by adding a DC-LAMP-derived lysosomal targeting sequence.

Dendritic cells modified *ex vivo* have been used in numerous clinical trials. The results of the investigator initiated studies performed in Brussels for the treatment of melanoma will be presented. But mRNA can also be used directly, i.e. by injection of naked mRNA in vivo to reprogram and load the professional antigen presenting cells in lymph nodes or at the tumor site. The latter approach is now being implemented in clinical studies.

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Nicola Tirelli graduated (1992) and later obtained a PhD (1996) in Chemistry at the University of Pisa (Italy). He held positions at the ETH Zurich (postdoc, then Oberassistent) before joining the UoM in 2003, where he now is part of the School of Health Sciences. Currently, he is director of the CDT in Regenerative Medicine and academic lead of the NorthWest Centre of Advanced Drug Delivery.
He is predominantly active in the molecular design of nanomaterials and injectable gels, for applications respectively in targeted delivery and in regenerative medicine.

Achievements and unsolved problems in the delivery of nucleic acids with chitosan/hyaluronic acid nanocarriers

The paper is about nanoparticles obtained via complexation between a cationizable polymer (chitosan) and anionic components (hyaluronic acid; nucleic acids).

Specifically, the presentation will focus on the influence that macromolecular variables (avidity between polyelectrolytes, degree of exposure and functionalization of hyaluronic acid) have on the CD44-mediated cell surface binding, on the internalization rate and on the transfection efficiency (with different nucleic acid payloads) of the nanoparticles.

A relatively high number of unexpected findings will be presented, which indicate how the process of receptor-mediated binding and internalization is still far from being completely understood; in particular, areas where quantitative information is still lacking are e.g. the degree of receptor clustering around nanoparticles, or the relation between macromolecular structure of the components and their endosomolytic activity.

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Dr. Richard Weiss has been working on generation of novel types of vaccines at the Department of Molecular Biology at the University of Salzburg, Austria for more than 15 years. After initially developing protective vaccines against infectious diseases such as Lyme disease and malaria, Dr. Weiss has subsequently specialized on prophylactic and therapeutic DNA and mRNA vaccination approaches for allergic diseases. In recent years, he focused on skin based vaccination and its applicability for specific immunotherapy, generation of DC targeting nanoparticles for cutaneous vaccination, and the influence of protein fold-stability on immunogenicity and allergenicity. Since 2012, he holds a position as Associate Professor at the Department of Molecular Biology.

Paving the way for prophylactic allergy gene vaccines –naturally acquired immunity as a template for vaccine design

Today, allergen specific immunotherapy is the only curative approach for treatment of type I allergies. Despite being in use for more than 100 years, efficacy is limited and the therapy is associated with side effects. Therefore, prophylactic vaccines that prevent development of allergies from the very beginning are seriously discussed. However, it is still an ongoing debate which type of immune response prophylactic allergy vaccines should induce. We have recently shown that in healthy individuals a broad spectrum of naturally acquired protective immune response types is employed, including "inflammatory" responses such as TH1 immunity. Gene vaccines have demonstrated to provide excellent protection from allergic sensitization in rodent models, and this protection was mainly dependent on inducing TH1 cells, thus mimicking one type of natural immunity. Due to their high safety profile, especially mRNA vaccines are promising candidates for prophylactic allergy vaccines. Our data clearly indicate that mRNA vaccination against allergens induces robust, long-lived memory responses, which can be recalled by allergen exposure without side effects. By targeting antigen expression to specific-cellular compartments, potential side effects can be avoided. Thus, mRNA vaccines fulfill the requirements for safe prophylactic vaccination against allergies without the need for booster immunizations.

PUBLIC LECTURE

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Philippe Roingeard est professeur de biologie cellulaire à la Faculté de Médecine et praticien hospitalier au CHU de Tours. Il a fait toutes ses études à l'Université François Rabelais de Tours, suivies d'un séjour postdoctoral de deux années et demi à l'Université de Harvard. Il est actuellement directeur de l'unité INSERM U966 (Virus des hépatites et du SIDA), de la Plateforme IBiSA de Microscopie Electronique de Tours et vice-Président de l'Université François Rabelais, en charge des Ecoles Doctorales et des relations avec la Comue. Ses travaux portent sur les hépatites virales B et C, et notamment sur la mise au point d'un vaccin bivalent contre ces deux virus. Il est auteur/co-auteur de plus de cent publications indexées dans PubMed. Il a obtenu le prix Drieu-Cholet de l'Académie Nationale de Médecine en 2014 et le prix Jean Valade de la Fondation de France en 2015 pour ses travaux.

Défi et challenge de la mise au point d'un vaccin contre le virus de l'hépatite C.

Le virus de l'hépatite C infecte plus de 180 millions de personnes dans le monde et environ 250 000 personnes en France. Il représente une cause majeure de maladies chroniques du foie, évoluant souvent vers la cirrhose et le cancer du foie. Ces nouvelles molécules antivirales ont permis de lutter de manière efficace contre ce virus mais elles restent extrêmement coûteuses. Même si elles contribuent de manière significative à faire reculer la maladie, les enjeux financiers font qu'elles ne pourront pas constituer l'unique solution pour éradiquer la maladie. Par ailleurs, de nombreux porteurs chroniques du virus ignorent être infectés. Si les traitements sont utilisés trop tard, ils peuvent éliminer le virus, mais ils restent inefficaces pour empêcher le foie de progresser vers une cirrhose et un cancer du foie. L'organisation mondiale de la santé (OMS) estime que tous les ans 3 à 4 millions de personnes sont nouvellement infectées par ce virus dans le monde. Pour toutes ces raisons, la mise au point d'un vaccin préventif de l'infection par le virus de l'hépatite C est un enjeu de santé publique important, à la fois pour se donner les meilleures chances d'éradiquer la maladie et pour diminuer les dépenses de santé liées à ce virus.

Reconnue internationalement dans la recherche sur les virus des hépatites et du VIH, l'U966 développe des axes de recherche fondamentale liée à la morphogenèse de ces virus, ou des aspects plus appliqués liés à leur dissémination et leur épidémiologie, ainsi qu'au développement de stratégies vaccinales innovantes. C'est d'ailleurs en étudiant les mécanismes de morphogenèse comparés des virus des hépatites B et C que cette équipe a eu l'idée de concevoir un vaccin bivalent contre ces deux virus. Ceci illustre comment une recherche fondamentale peut déboucher sur des applications médicales. La Région Centre Val de Loire a déjà été à l'honneur avec la mise au point du premier vaccin contre l'hépatite B, par l'équipe du Professeur Philippe Maupas, il y a plus de trente ans. Dans la continuité de ces travaux, Philippe Roingeard et son équipe ont établi le concept d'un vaccin contre l'hépatite B modifié, incorporant également des constituants du virus de l'hépatite C, capable d'induire une réponse immunitaire contre les deux virus.

ORAL PRESENTATIONS

Thomas Démoulins

Fine-tuning of polyplex formulations to improve efficacy of self-replicating RNA vaccines

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The major limitations with large and complex self-amplifying RNA vaccines (RepRNA) are RNase-sensitivity and inefficient uptake for translation by dendritic cells (DCs). We recently overcame these issues by condensing RepRNA with polyethylenimine (PEI) to formulate polyplexes. Herein, we showed that fine-tuning of polyplex structure (with three parameters investigated: (1) PEI molecular weight (MW); (2) RepRNA:PEI (weight:weight) ratio; (3) inclusion of cell penetrating peptides (CPPs)) strongly modulates RepRNA functionality. Indeed, 7 commercially available linear PEIs (MW 2,500 – 250,000) were assessed and classified as strong, intermediate or low for their aptitude to bind / protect / deliver RepRNA into porcine bDCs. Then, when (Arg)9 or TAT(57-57) were included in some polyplex formulations, the translation readouts were totally opposite depending RepRNA structural gene (E2) or gene of interest (GOI) (luciferase, HA or NP) were considered. Altogether, we ended up with formulations [Rep/PEI-4,000 (1:3)] and [Rep/PEI-40,000 (1:2)/$(Arg)_9$] and confirmed their efficacy in porcine SK6 cell line, as well as porcine and human DCs. These two formulations were successfully employed *in vivo* in mice and pigs where specific anti-GOI $CD8^+$ T and $CD4^+$ T-cell responses were seen, confirming delivery to DCs for translation of encoded GOIs. This study validates the importance of predefining the best synthetic vaccine formulations *in vitro*, for ensuring the desired immune activation *in vivo*.

Keywords: Replicon-RNA; polyethylenimine; polyplexes; cell penetrating peptides; influenza vaccines; T-Cell immune response

Federico Perche

Improved brain expression of anti-amyloid β scFv by complexation of mRNA including a secretion sequence with PEG-based block catiomer.

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ABSTRACT: Background: The ever-increasing number of people living with Alzheimer's disease urges to develop more effective therapies. Despite considerable success, anti-Alzheimer immunotherapy still faces the challenge of intracerebral and intracellular delivery. This work introduces *in situ* production of anti-amyloid beta (Aβ) antibody after intracerebral injection of PEG-PAsp(DET)/mRNA polyplexes as a novel immunotherapy approach and a safer alternative compared to high systemic antibodies doses or administration of adenovirus encoding anti- Aβ antibodies.

Methods: We used mRNA encoding three different Aβ-specific scFV with a secretion signal for passive immunotherapy. scFv contained a 6xHis-tag for immuno-detection. The secretion signal from IL2 (IL2ss) was added to allow extracellular engagement of senile plaques. Aβ affinity of scFv was measured by surface plasmon resonance. To allow intracellular delivery, scFv were administered as polyplexes formed with our smart copolymer PEG-PAsp(DET) (polyethyleneglycolpoly[N9-[N-(2-aminoethyl)-2-aminoethyl]aspartamide). We evaluated scFv expression *in cellulo* by Western blot and ELISA, their ability to disaggregate amyloid aggregates by thioflavine T assay. Moreover, *in vivo* expression and therapeutic activity were evaluated in a murine amyloidosis model, by anti-6xHis-tag ELISA and anti- Aβ ELISA, respectively.

Results: The selected anti-amyloid beta scFv showed affinity towards Aβ and disaggregated Aβ fibers *in vitro*. Whereas both DNA and mRNA transfection led to scFV expression in cancer cells, only mRNA led to detectable scFv expression in primary neurons. In addition, the use of IL2ss increased by 3.4-fold scFv secretion by primary neurons over mRNA polyplexes devoid of secretion signal. *In vivo*, a 3 to 11-fold of intracranial scFv levels was measured for mRNA compared to DNA polyplexes and higher *in vivo* scFv levels were obtained with mRNA containing IL2ss over non-secreted mRNA. Intracranial injection of anti- Aβ mRNA polyplexes with IL2ss resulted in 40 % Aβ decrease in an acute amyloidosis model; with no decrease detected with control scFv mRNA nor DNA polyplexes. However, no Aβ decrease was detected in a more challenging transgenic model of Alzheimer's disease

Conclusion: Our results introduce a concerted approach not only for Alzheimer's disease treatment but also for immunotherapy against neurological diseases. The effectivity of our platform required the intracranial delivery of anti- Aβ scFv as mRNA not DNA, as mRNA with an IL2ss secretion sequence to favor engagement of Aβ in the amyloidosis model, complexation with a smart copolymer for efficient transfection of primary neurons and to achieve detectable mRNA expression in the brain during 48h. Amyloid burden decrease in an acute amyloidosis model was only achieved when these three factors (mRNA coding scFv, smart copolymer, IL2ss) were integrated into a single formulation.

Lucie Pigeon

Messenger RNA bioproduction

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The increasing number of clinical trials proves the potentiality of these molecules to be considered as a new class of biopharmaceuticals. Messenger RNA offers a strong safety compared to DNA because it cannot be integrated in host genome. The translation machinery being located in the cytosol, mRNA expression does not require nuclear import which is of benefit for hard to transfect and non-dividing cells.

In eukaryotic cells, the translation efficiency of mRNA is relied on its mature structure composed of (i) cap –m7Gppp; (ii) 5'untranslated region; (iii) protein-encoding open reading frame; (iv) 3'untranslated region; (v) poly(A)tail. Therapeutic mRNA used so far are obtained using plasmid construct that could be in vitro transcribed *via* enzymatic reaction based on bacteriophage T7 or SP6 polymerase. Different strategies have been proposed to improve mRNA synthesis for better translation efficiency. They are based on using a cap structure analogue, optimized codon usage or specific 3' and 5'UTR known to improve its stability. Moreover, exogenous mRNA can be sensed by pattern recognition receptors (PRRs) as viral RNA activating immune mechanisms and decrease of the translation efficiency. Such adverse effects could be reduced or prevented by using modified nucleotides during mRNA in vitro production. These last years, mRNA has been proven to be efficient for vaccination, for production of induced pluripotent stem cells and even can be used to encode nucleases such as ZFN, TALEN, and CRISPR/Cas9 for genome editing. For regenerative medicine, they could be exploited instead of protein therapy.

Despite advantages of synthetic mRNA production, there are some limitations as the number of reagents and step reactions required, synthesizing mRNA with large size could be challenging due to polymerase fidelity etc. We sought to find an alternative of this technology production. The challenge was to develop a strategy that allows mRNA production with a mature structure able to be efficiently translated in human cells. Since yeast cells share many cellular processes with mammalian cells and are recognized as safe, we chose them as cell factory. We will present how we did performed yeasts genetic engineering to produce in demand mRNA of interest and to target them in a specific compartments that are easy to purify. The bio-produced mRNA was efficiently expressed in dendritic cells.

Rein Verbeke

Messenger rna lipoplex-mediated cancer immunotherapy: finding balance between RNA's expression and immunogenicity

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Introduction: Messenger RNA encoding tumor antigens has great potential as active pharmaceutical ingredient for therapeutic cancer vaccination. In 2016, several research groups published on lipid carriers for mRNA delivery, as they package the mRNA to provide protection against enzymatic degradation while aiding the transport of mRNA to antigen presenting cells *in situ*[1,2,3]. mRNA lipoplexes seem promising, but are linked to high release of type I interferons (IFN). Interestingly, no consensus has been reached on whether this type I IFN response is beneficial or rather counteracts the vaccine's efficacy and safety. Therefore we designed a lipid carrier to package chemically modified mRNA for systemic delivery, and investigated if we could obtain higher antigen expression *in vivo* while replacing the type I IFN response by a more controllable and desirable adjuvant effect.

Experimental methods: In this study the potential of three different mRNA lipid formulations was evaluated after systemic administration in C57BL/6 mice. More specifically, a comparison regarding bio-distribution, mRNA's transfection efficiency and immunogenicity was made between lipid particles carrying (1) unmodified mRNA, (2) nucleoside-modified mRNA (5-methylcytidine, pseudouridine), and (3) the nucleoside-modified mRNA combined with the adjuvant monophosphoryl lipid A (MPLA).

Results and Discussion: The use of modified mRNA highly improved the transfection efficiency, resulting in detectable mRNA expression levels in lungs, spleen, and lymph nodes. The different cargos did not influence either the particle's physical properties, or impair the targeting of DCs *in vivo*, indicating that the choice of mRNA construct directly affects the protein expression. Cytokine patterns in blood and the phenotype of spleen DCs showed that unmodified mRNA strongly induces type I interferons, which leads to efficient immune activation, but results in much lower mRNA expression levels. Importantly, we give evidence that well-known adjuvants, such as MPLA, can be co-delivered with mRNA, by co-encapsulating the adjuvant in the lipid particles. Planned experiments need to proof if we can compensate the low immunogenicity of modified mRNA by addition of other adjuvants, such as MPLA, to obtain a mRNA vaccine with a desirable vaccine's efficacy and safety, independent of type I IFNs.

Conclusion: Since the use of immunogenic mRNA has previously been the focus for mRNA vaccine strategies, we suggest with this study that combinations of modified mRNA with well-known immune adjuvants, such as MPLA, could probably further increase both the efficacy and safety of mRNA lipoplex-mediated cancer immunotherapy.

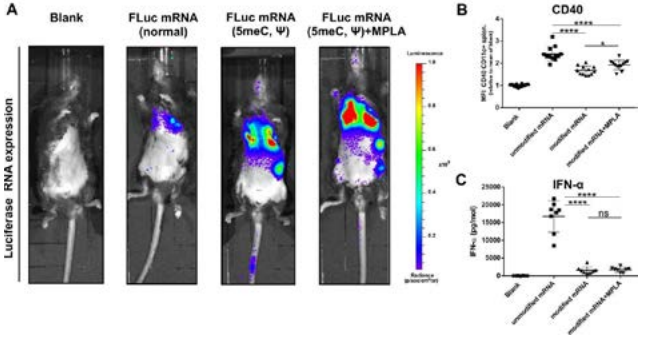

Figure 1: (A) luminescence images of BL/6 mice 6h after the injection of unmodified mRNA lipoplexes, modified mRNA lipoplexes or modified mRNA lipoplexes with MPLA (10µg mRNA). (B) CD40 expression of CD11c positive splenocytes 24h after treatment. (C) IFN-α levels of blood samples collected 6h after injection.

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